Today’s agenda

Aplastic Anemia – general overview
Non-transplant treatment options
Novel agents and active research

AGE AT DIAGNOSIS
Aplastic Anemia Admissions to NIH Clinical Center

*NATURAL HISTORY* OF APLASTIC ANEMIA

Severity Criteria (two of three):
- platelets <20k/μL
- reticulocytes <1% (60k/μL)
- ANC <500/μL
Super-severe: ANC <200/μL

Camilla et al. Blood 52:504, 1979
Causes of Aplastic Anemia

Most of the cases of Aplastic Anemia have no identifiable cause.
Pregnancy, eosinophilic fasciitis, and seronegative hepatitis are associated with AA.
Drugs and chemicals have been reported as well (Benzene, Chloramphenicol).

All identifiable causes explain very few cases of AA.

Pathophysiology of Aplastic Anemia

- Immune attack
- Stem cells
- Hematopoietic progenitors

- 1960’s → 10% survival in 1 year
- 2010 → 90% survival in 1 year

Immunosuppressive therapy

- Anti-thymocyte globulin (ATG)
  - Horse
  - Rabbit
- Cyclosporine (CsA)
- Campath
- Others

• Immunosuppressive therapy
• Bone marrow transplantation
• Supportive care
• Novel agents
**Immunosuppressive therapy**

- First line of treatment in adults
- Salvage for treatment-refractory patients
- Treatment for relapsed disease

**PROGRESS IN IMMUNOSUPPRESSIVE THERAPIES FOR SEVERE APLASTIC ANEMIA**

<table>
<thead>
<tr>
<th>Era</th>
<th>Drug</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s</td>
<td>corticosteroids</td>
<td>~10% (occasional)</td>
</tr>
<tr>
<td>1970s</td>
<td>ATGs</td>
<td>40-50%</td>
</tr>
<tr>
<td>1980s</td>
<td>ATG plus CSA</td>
<td>60-70%</td>
</tr>
</tbody>
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PROGRESS IN IMMUNOSUPPRESSIVE THERAPIES FOR SEVERE APLASTIC ANEMIA

- **Era** | **Drug** | **Response**
- 1960s | corticosteroids | ~10% (occasional)
- 1970s | ATGs | 40-50%
- 1980s | ATG plus CSA | 60-70%

RESPONSE OF SEVERE APLASTIC ANEMIA TO INTENSIVE IMMUNOSUPPRESSION

Response at 3 months and survival

INTENSIVE IMMUNOSUPPRESSION FOR SAA COMPARISON OF RESULTS

- **Study** | **Years** | **N** | **Median Age (years)** | **Response** | **Relapse** | **Clonal Evolution** | **Survival** |
- German | 1965-1969 | 84 | 32 | 55% | 10% | 6% | 58% at 11 yrs |
- NIH | 1991-1996 | 122 | 35 | 51% | 15% | 13% | 50% at 7 yrs |
- EGBMT | 1991-1998 | 100 | 18 | 77% | 12% | 11% | 87% at 5 yrs |
- Japan | 1992-1997 | 119 | 9 | 68% | 32% | 6% | 88% at 3 yrs |
- German/Austrian | 1993-1997 | 114 | 9 | 77% | 12% | 6% | 87% at 4 yrs |
- Japanese | 1995-2000 | 101 | 54 | 73% | 42% | 8% | 88% at 4 yrs |
- NIH | 1999-2005 | 184 | 35 | 52% | 37% | 9% | 80% at 4 yrs |
- EGBMT | 2002-2006 | 192 | 46 | 70% | 30% | 4% | 76% at 6 yrs |
- NIH | 2003-2005 | 77 | 28 | 57% | 36% | 10% | 90% at 3 yrs |
- NIH | 2005-2010 | 100 | 28 | 60% | 28% | 21% | 96% at 3 yrs |

NEW DIRECTIONS IN TREATMENT FOR APLASTIC ANEMIA

- Add to horse ATG + CsA platform
  - G-CSF (Neupogen)
  - Mycophenolate mofetil
  - Sirolimus
  - Long course immunosuppression
- Augment initial lymphocytotoxicity
  - Horse ATG
  - Rabbit ATG
  - Campath
A Randomized Trial of H-ATG vs. R-ATG in SAA

Patients and Methods

- 120 consecutive patients (60 per arm)
- NIH Clinical Center
- 1:1 randomization
- Primary objective – response at 6 months

Scheinberg et al. NEJM 2011

A Randomized Trial of H-ATG vs. R-ATG in SAA

Hematologic Responses at 3 and 6 months

<table>
<thead>
<tr>
<th></th>
<th>Horse ATG</th>
<th>Rabbit ATG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>37/60 (62%)</td>
<td>20/60 (33%)</td>
<td>0.003</td>
</tr>
<tr>
<td>6 months</td>
<td>41/60 (68%)</td>
<td>22/60 (37%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Blood Count Recovery in Responders

Alemtuzumab (Campath-1H)

- Anti-CD52 Antibody
- Murine hypervariable regions fused into human IgG1
- CD52 expressed:
  - B and T cells
  - NK cells, dendritic cells
  - Monocytes, macrophages
  - Plasma cells, Eos
- No CD52 expression on:
  - RBCs, platelets
  - Hematopoietic stem cells

Ravandi and O'Brien, Cancer Invest. 2007 24: 718-725
Hernández-Campo PM, Cytometry B Clin Cytom. 2006 70:71
SECOND IMMUNOSUPPRESSION FOR REFRACTORY SAA

<table>
<thead>
<tr>
<th>Treatment arm (N=54)</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>rabbit ATG (N=27)</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>alemtuzumab (N=27)</td>
<td>10 (37%)</td>
</tr>
</tbody>
</table>

RELAPSE AFTER ATG + CSA

<table>
<thead>
<tr>
<th>Years post-relapse</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on CsA</td>
<td>20/22</td>
<td>19/20</td>
<td>14/18</td>
<td>11/17</td>
<td>11/14</td>
<td>7/11</td>
<td>4/7</td>
</tr>
<tr>
<td></td>
<td>(86%)</td>
<td>(91%)</td>
<td>(78%)</td>
<td>(65%)</td>
<td>(79%)</td>
<td>(64%)</td>
<td>(57%)</td>
</tr>
</tbody>
</table>

Retreatment with rabbit ATG + CsA Post-1st relapse → 2/3 response

CAMPATH IMMUNOSUPPRESSION FOR RELAPSED SAA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campath (N=25)</td>
<td>14 (56%)</td>
</tr>
</tbody>
</table>

INITIAL BLOOD COUNTS PREDICT RESPONSE TO IMMUNOSUPPRESSION AND SURVIVAL

Probability of response according to age

<table>
<thead>
<tr>
<th>Number of</th>
<th>Response at 6 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients (%)</td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>H-ATG</td>
<td>316 (100)</td>
<td>194</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18</td>
<td>78 (25)</td>
<td>58</td>
</tr>
<tr>
<td>18 to 60</td>
<td>187 (59)</td>
<td>109</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>51 (16)</td>
<td>27</td>
</tr>
</tbody>
</table>
Survival Probability in Children

Overall Responders to IST

Survival in refractory SAA
1990s

Improved Survival Over Time

Improved Survival Over Time

Improved Survival Over Time

HEMATOPOIETIC GROWTH FACTORS AS THERAPY FOR SAA

Ganser A et al, Blood 1990; 76:1287: IL-3 pilots
Kojima S et al, Blood 2002;100:786: G-CSF

Tichelli A et al, Blood 2011; 117:4434: G-CSF shows no survival benefit
ELTROMBOPAG FOR REFRACTORY SEVERE APLASTIC ANEMIA

- SAA with plt ≤ 30K/μL
- Refractory to ATG/CSA

Eltrombopag 50 mg daily

Dose escalation every 2 weeks to 150 mg daily

Hematologic response at 3 months

Responders followed monthly, on drug

Hematologic Response Criteria

- Platelets: >20K/μL increase, or transfusion-independence
- RBCs: > 1.5 g/dL increase in Hb, or transfusion-independence
- ANC: >100% increase if severe neutropenia, or >500/μL increase

NIH Protocol 09-HD32104; ClinicalTrials.gov identifier: NCT00922883

REFRACTORY SAA ELTROMBOPAG STUDY RESULTS

Censure date 11/1/2011

Median follow up 13 months (range 4-28 months)

26 patients enrolled

1 patient ineligible, not treated

11 responders (44%)

- 9 platelet responses
- 2 hemoglobin responses
- Additional 4 at >16wks
- 4 neutrophil responses
- Additional 3 at >16wks

25 evaluable patients

14 non-responders

- 10 stable disease
- 2 died of progression
- 2 clonal evolution to MDS
- 1 died
- 1 HSCT

BONE MARROW CELLULARITY AT ONE YEAR

Pre-treatment

Post-treatment

Platelets

Neutrophils

Hemoglobin

MULTI-LINEAGE HEMATOLOGIC RESPONSES TO ELTROMBOPAG

Platelets

Hemoglobin

Neutrophils

INSIGHTS INTO SAA PATHOPHYSIOLOGY FROM ELTROMBOPAG RESPONSIVENESS

- Eltrombopag can promote tri-lineage hematopoiesis in SAA patients refractory to IST
- 44% clinical response rate
- Transfusion independence
- Well-tolerated

- Eltrombopag stimulation may expand the HSC pool in humans

- Addition of Eltrombopag early in SAA may increase response rate, decrease time to response, prevent HSC depletion, and avoid clonal progression

SUMMARY
ELTROMBOPAG FOR MODERATE AA
NHLBI 09-H-0154
clinicaltrials.gov NCT00922883
Eltrombopag, dose escalation to 150 mg QD by mouth
>18 years old; platelet count <30,000/uL
Assessment by blood counts and BM at 3 and 6 months

Horse ATG + CSA and ELTROMBOPAG
for treatment-naïve SAA
NHLBI 12-H-xxxx
Add eltrombopag to existing horse ATG + CSA platform will increase overall response and decrease relapses

TELOMERE STRUCTURE AND BIOLOGY
- Cap chromosome ends
- Tandem TTAGGG repeats
- Bound to array of proteins: telomerase complex
- Forms higher order chromatin T loop
- Shields 3’ end to prevent recognition as a DNA ‘break’ by non-homologous end-joining machinery
- TTAGGG loss with proliferation: “end replication problem”

TELOMERE LENGTH IN TERT/MUTATION LEUCOCYTES

TELOMRES AND BONE MARROW FAILURE
DYSKERATOSIS CONGENITA

N = 168 consecutive patients on NIH IST protocols
Mean age = 34 years (4-82 years)
no relationship to response to treatment (PR, CR)
RELAPSE RATE BY TELOMERE QUARTILES

EVOLUTION RATE BY TELOMERE LENGTH

MONOSOMY 7 EVOLUTION BY TELOMERE LENGTH

SURVIVAL PROBABILITY BY TELOMERE LENGTH

SHANK’S DISEASE™ IN A MENNONITE FAMILY

LATE PRESENTATION OF DYSKERATOSIS CONGENITA

Early onset of graying (20’s) and low platelets
Thrombocytopenia, gray hair, very short telomere, TERT mutation

37 y/o US Army officer in Afghanistan
tongue ulcer, diagnosed as squamous cell carcinoma
single round of chemotherapy and radiation resulted in unexpected extreme,
persistent pancytopenia. Later, pulmonary metastases
novel Val329Gly mutation in DKC1

Peripheral Blood Telomere Length

Thrombocytopenia, gray hair, very short telomere, TERT mutation

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Early onset of graying (20’s) and low platelets
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Danazol for telomeropathy

11-H-0209: “Danazol for Genetic Bone Marrow and Lung Disorders”

ClinicalTrials.gov identifier: NCT01441037

http://clinicaltrials.gov/ct2/show/NCT01441037?term=danazol+for+telomere&rank=1

15 patients enrolled in first 6 months.

First patient enrolled on 08/19/2011

First 6 months – no drug-related toxicities.

( Minimal elevation in LFTs in almost all patients and controllable headaches in 4 patients).